REMARKS

Applicants have amended the claims to more particularly define the invention taking into consideration the outstanding Official Action. It is understood that the provisional obviousness double patenting rejection is held in abeyance until one of the applications is allowed at which time one application will be allowed and the other subject to a non-provisional obviousness type double patenting rejection in accordance with USPTO procedure. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 US 112 and are clearly patentable over the references of record.

Applicants first wish to note that the key change in the amended claims is that the first independent claim, claim 50, is restricted to measurement of the TCII protein component, as a means of assessing the holoTCII level in the pre-treated sample, with the "or cobalamin" wording deleted from the claim without prejudice or disclaimer. The alternative embodiment, wherein cobalamin is measured, is now recited in new claims 73, and further dependent claims 74 and 75 which are specific to that method and as fully supported by the specification as originally filed. Certain of the previous dependent claims are correspondingly deleted without prejudice or disclaimer.

The rejection of claims 50-57, 65-68, and 71 under 35 USC 103(a) as being obvious over Herbert in view of Van Kapel et al and further in view of Jacobsen et al has been carefully considered but is most respectfully traversed in view of the amendments to the claims.

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a

reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

Applicants most respectfully submit that the amendment made to claim 50 is responsive to all of the obviousness arguments presented by the Examiner in the last Office Action. Specifically, none of the prior art cited carries out a measurement of the TCII protein component of a holo-TCII containing sample, whereby to assess the holo-TCII content. This step is important in the context of the complete assay because it is only in combination with the apo-binding pre-treatment step that assessment of the TCII component can provide a measure of holo-TCII in the originating sample. Thus, the combination of apo-prebinding and assessment of TCII content gives a new and simpler approach to holo-TCII measurement which is not suggested by the prior art.

Applicants most respectfully submit that no cited document provides a method for holo-TCII assessment comprising a pre-binding step to remove apo-TCII (see below) and no cited document utilizes measurement of the TCII protein to represent the holo-

TCII level in the sample. This latter shortcoming in probability arising from the fact that without an apo-prebinding step, measurement of TCII levels does not provide any information on holo-TCII content. Among the contributions of the present inventors is the realization that by incorporating an apo-prebinding step into a holo-TCII assay, measurement of the remaining TCII content will represent the original holo-TCII level.

In view of the above amendment, the Examiner's rejections on the grounds of obviousness are considered moot in respect of claims 50-70, since no reference cited teaches or suggests the measurement of the TCII protein component in an assay for holo-TCII, and most significantly, no reference indicates the advantageous combination of pre-treatment to remove (or render non-reactive) the apo-TCII component, followed by measurement of the remaining TCII in the sample in accordance with the presently claimed invention. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

With regard to new claims 73 to 75, these relate to the embodiment of the invention wherein apo-TCII is removed or rendered non-reactive by pre-binding, followed by analysis of the cobalamin component of the holo-TCII remaining in the sample, whereby to assess the holo-TCII content. The Examiner has considered the Applicant's previous submissions with regard to lack of teaching of an apo-TCII pre-binding step, and indicates that these arguments were persuasive. At the first paragraph of page 12 of the Office Action, however, the Examiner then indicates that references to Van Kapel and Jacobsen have now been added "to make this limitation obvious". However, Applicants most respectfully traverse this statement for the following reasons.

Applicants most respectfully wish to point out that in order for the presence of a step relating to the pre-binding of apo-TCII to be obvious, the prior art should teach not

only that binding of apo-TCII is known, but further that there is some motivation by which a skilled artisan would derive an incentive to combine this with the teaching of a compatible holo-TCII assay, so as to provide the currently claimed method.

In the present case, Van Kapel provides for no selective binding of apo-TCII over holo-TCII. The method of Van Kapel simply attempts to allow both the apo-TCII and holo-TCII fractions to be measured. In this method, all of the TCII is bound to heparin. If the cobalamin bound to the heparin is released from, these beads and measured then the holo-TCII content may allegedly be determined, where as binding of further cobalamin onto the beads is reported to indicate the apo-TCII component. No selective binding of apo TCII is taught, and if the method of Van Kapel were effective then none would be needed. As a result, no teaching towards such as step can be provided by this citation. It is essential to distinguish separate *measurement*, which is provided by Van Kapel but is not claimed, from separate *binding*, which is claimed but not provided by Van Kapel.

Applicants acknowledge that Jacobsen uses a method involving synthesis by the binding of apo-TCII to cobalamin coated beads, but would respectfully point out that the teaching of Jacobsen is in no way related to assays for holo-TCII. Jacobsen relates to a method for determining whether particular cell lines express receptors for the TCII protein, and in doing so Jacobsen must create beads having immobilised TCII. The method chosen is by immobilizing cobalamin onto beads and then binding TCII to that cobalamin. This cannot relate to a step in an assay for holo-TCII, because the beads having immobilised cobalamin analogues attached thereto are simply intermediates in the production of bead-immobilised TCII. Jacobsen places no particular emphasis or significance on this intermediate, and neither would a man of skill in the art. There is absolutely nothing that would teach towards an apo-TCII pre-binding step in a holo-TCII analysis method, or towards the combination of this reference with any of the others cited.

Applicants most respectfully submit that the teaching of an apo-separation step as a tool to simplify a holo-TCII assay method is the essential starting point if a holo-TCII assay method comprising such a step is to be obvious. Applicants most respectfully submit that no such teaching can be found in any document known to date and as previously note, Applicants' teaching may not be used to modify the prior art to arrive at the claimed subject matter.

The further rejection of claims 62-64 under 35 USC 103(a) as being unpatentable over Herbert in view of Van Kapel et al. and further in view of Jacobsen et al for the reasons applied to claims 50-57, 65, 66 and 71 and further in view of Hoyle et al has been carefully considered but is most respectfully traversed in view of the further amendments to the claims and above comments. The Houyle et al reference does not overcome the deficiencies of the primary references for the reasons discussed above. Accordingly it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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